TRAFFICKING

RNA granules take a ride on lysosomes

Credit: Getty/Malte Mueller

Localized protein synthesis requires intracellular RNA transport, whereby mRNAs are trafficked within RNA granules — membraneless organelles that form through liquid–liquid phase separation. The mechanisms involved in this transport are poorly understood. Liao et al. now show that in mammalian cells, RNA granules are trafficked by 'hitchhiking' on lysosomes.

The authors established that in the human U2OS cell line and in primary rat cortical neurons RNA granules associate with the surface of lysosome-like organelles and traffic on them. They then identified annexin A11 (ANXA11) as a protein that interacts with both granules and lysosomes, and thus could serve as a tether between these organelles.

In U2OS cells ANXA11 partitioned to RNA granules in a manner dependent on the N-terminal low-complexity region, which mediates its liquid–liquid phase separation. The interaction with the lysosome, in turn, depended on the C-terminal annexin domains of ANXA11, which bind — in a calcium-dependent manner — to endolysosomal phosphoinositides.

ANXA11 was sufficient to drive association between RNA granules and lysosome-like vesicles in vitro. ANXA11 also co-localized with motile lysosome–RNA granule complexes in neurons, where it was required for unperturbed RNA granule hitchhiking on lysosomes and for efficient RNA delivery to the distal parts of the cell.

Mutations in the gene *ANX11* are linked to neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). ALS-causing mutations interfered with phase separation dynamics of ANXA11 and reduced its ability to partition to RNA granules, and also impeded ANXA11 binding to lysosomal membranes. Accordingly, expression of ANXA11 mutants perturbed RNA granule–lysosome contacts, reduced the number of hitchhiking events and interfered with intracellular mRNA transport in neurons, both in culture and in zebrafish larvae.

ALS-causing mutations interfered with phase separation dynamics of ANXA11

In summary, efficient mRNA trafficking is supported by tethering of RNA granules to motile lysosomes through ANXA11, which is regulated by phase separation and calcium signalling. Deregulation of these mechanisms could contribute to neurodegeneration.

Paulina Strzyz

ORIGINAL ARTICLE Liao, Y.-C. et al. RNA granules hitchhike on lysosomes for long-distance transport, using annexin A11 as a molecular tether. *Cell* **179**, 147–164 (2019)

GENE REGULATION

G-tracts give PRC2 the boot

Polycomb repressive complex 2 (PRC2) interacts with chromatin to trimethylate histone H3 at Lys27 (H3K27me3) and repress gene expression, a process that is often dysregulated in cancer. Beltran et al. now reveal that PRC2–chromatin binding is regulated by chromatin-associated G-quadruplex (G4)-containing RNA, which binds PRC2, removes it from chromatin and reactivates gene expression.

The authors previously showed that PRC2 binds pre-mRNAs in mouse embryonic stem cells. Here, bioinformatics approaches suggested that PRC2 interacts with G-tracts within pre-mRNA and preferentially with G-tracts that form G4 structures. Indeed, in vitro, removal of the G4-forming G-tract from *PIM1* RNA reduced its interaction with PRC2, and PRC2–*PIM1* RNA binding was strongest in buffer permitting the formation of G4 structures. Thus, PRC2 interacts with G4 structures.

G-tracts can reactivate PRC2-repressed genes

Of note, G4 structures inhibited PRC2–nucleosome interactions in vitro, as the presence of generic G4-forming RNA or of *PIM1* RNA prevented interaction of the PRC2 catalytic core (which includes the methyltransferase EZH2) with substrate nucleosomes and removed it from nucleosomes to which it was already bound. To confirm that G4 structures removed PRC2 from nucleosomes in vivo the authors used nuclease-deactivated Cas9 in NIH3T3 cells to tether, to the 5′ end of the PRC2 target gene *Fgf11*, an artificial G-tract RNA or a G-tract RNA encoded by *Fgf11*. These G-tracts reduced binding of PRC2 to, and H3K27me3 at, *Fgf11* compared with controls. Furthermore, PRC2 was shown to move from chromatin to pre-mRNA upon $HRAS^{V12}$-mediated activation of its target genes, and also to move from chromatin to tethered G-tract RNA in the absence of $HRAS^{V12}$, indicating that PRC2 moves from chromatin to RNA upon gene activation.

Finally, Beltran et al. asked whether G-tract RNA could reactivate *CDKN2A* (which encodes the tumour suppressor p16), which is adversely silenced by PRC2 in malignant rhabdoid tumours (MRTs). Indeed, targeting G-tracts to *CDKN2A* in MRT cells depleted the gene of PRC2 and H3K27me3, reactivated it and increased p16 levels to those achieved by the non-specific EZH2 inhibitor EI1.

Credit: Image Source/Alamy Stock Photo

Thus, this study shows that G-tracts can reactivate PRC2-repressed genes and highlights their potential to do this at specific genes in cancer.

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ORIGINAL ARTICLE Beltran, M. et al. G-tract RNA removes Polycomb repressive complex 2 from genes. *Nat. Struct. Biol.* https://doi.org/10.1038/s41594-019-0293-z (2019)